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Phase 1b/2a safety and tolerability study of bemcentinib (BEM) with pembrolizumab/carboplatin/pemetrexed in subjects with untreated advanced or metastatic non- squamous non-small cell lung cancer (NSCLC) without/with a STK11 mutation

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BACKGROUND

The combination of platinum chemotherapy, pemetrexed and pembrolizumab (CIT) has become a standard of care as first line (1L) treatment in patients with non-squamous (NS) NSCLC. Despite improvements in response rates and survival, the emergence of primary or acquired resistance limits its efficacy.

STK11/LKB1 mutations (STK11m) are common (˜20%) in NSCLC and are associated with a poorer prognosis, irrespective of treatment modality, thus representing a high unmet medical need.[1-3] The phenotypic characteristics of STK11 mutated tumors (ie. high cellular stress and immune evasion) drive increased levels of AXL activation (Figure 1).

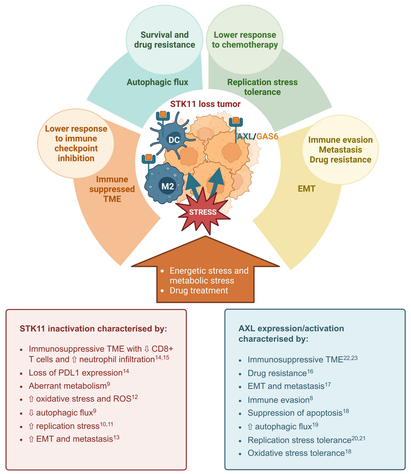


Figure 1: AXL is a key driver of survival and drug resistance in NSCLC tumors

Abbreviations: EMT=Epithelial-mesenchymal transition; ROS=Reactive oxygen species; DC=Dendritic cell; TME=Tumor microenvironment

AXL, a member of the TAM family of receptor tyrosine kinases, is activated in response to inflammation, hypoxia, cellular stress or drug treatment.[4-8] Tumor cells use the AXL pathway to sense stress and trigger molecular mechanisms to ensure survival or escape from the toxic environment (Figure 1). AXL is expressed in tumor cells, where it enhances survival, as well as in innate immune cells where it drives immune suppression.

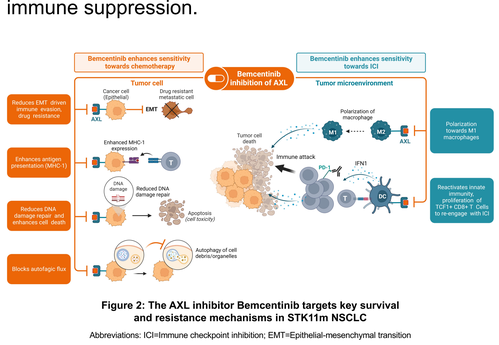


Figure 2: The AXL inhibitor Bemcentinib targets key survival and resistance mechanisms in STK11m NSCLC

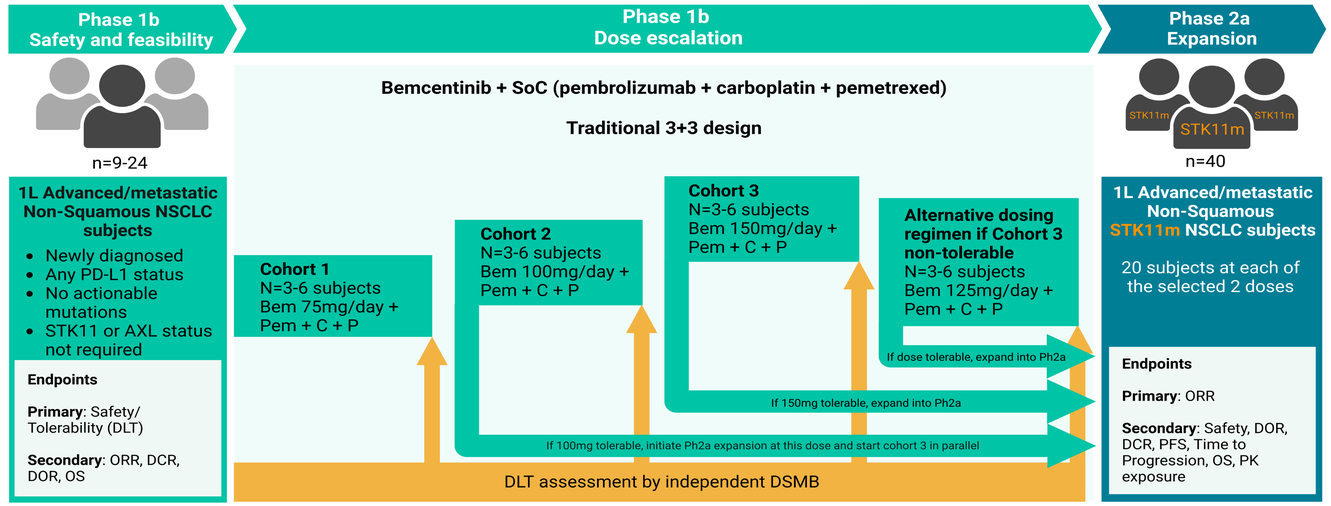
Abbreviations: ICI=Immune checkpoint inhibition; EMT=Epithelial-mesenchymal transition

Bemcentinib, (BEM) a selective AXL inhibitor, targets key survival and resistance mechanisms within the tumour and the microenvironment of NSCLC tumors (Figure 2). Importantly, AXL inhibition with BEM potentiated the efficacy of combined chemo-immunotherapy in models of NSCLC and BEM has been shown to sensitize STK11m NSCLC to immune checkpoint inhibitors in preclinical studies.[22]

In summary, based on supportive *in vitro* and *in vivo* pharmacology in NSCLC cells and animal models, as well as preliminary clinical data, the addition of BEM to CIT has the potential to improve the 1L treatment outcomes of NSCLC patients, particularly in tumors harboring STK11m.

STUDY DESIGN

BGBC016: open-label, multi-centre Ph1b/2a study in 1L NSCLC patients with STK11 mutations



Dosing Regimen Phase 1b/2a
Bem daily (oral) + Pem + C + P q21 days X 4 cycles
Followed by Maintenance: Bem daily (oral) + Pem q21 days + P q21 days up to 2yrs

Abbreviations: 1L=first line; Bem=bemcentinib; C=carboplatin; DC=doublet chemotherapy; DCR=disease control rate; DLT=dose limiting toxicity; DOR=duration of response; DSMB=data safety monitoring board; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; Perm=pembrolizumab; P=pemetrexed; PFS=progression free survival; PK=pharmacokinetics; SoC=Standard of care.

Aims

To assess the safety, tolerability, and preliminary anti-tumor activity of BEM in combination with CIT as 1L treatment in NS-NSCLC patients without actionable mutations.

Main Eligibility Criteria

- Newly-diagnosed patients with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) NS-NSCLC
- Absence of actionable mutations
- Any PD-L1 status
- STK11 mutation required only for ph2a

Safety Review

An independent data safety monitoring board (DSMB) will review the safety data at end of the DLT assessment period (first 21 days of cycle 1 for each patient) and will recommend the BEM doses for the phase 2a expansion.

Duration of the Study

Screening: up to 28 days

Treatment: up to 2 years

Follow-up: up to 2 years

The trial is currently enrolling patients in the phase 1b in the US; recruitment for the phase 2a is planned to open in Q2 2023 in Europe and US.

EudraCT 2019-003806-28/NA/124645 | ***NCT05469178***

RRV has served on advisory boards for Bristol-Myers Squibb, Astrazeneca, Merck, Boehringer Ingelheim, BerGenBio, Merus, Novocure, G1 Therapeutics, Regeneron; on steering committee for Novartis; on unbranded speaker's bureau of Astrazeneca; received consulting honorarium from Beigene. *Study sponsored by BerGenBio.*

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